Brugada syndrome: update and future perspectives

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ABSTRACT

Brugada syndrome (BrS) is an inherited cardiac disorder, characterised by a typical ECG pattern and an increased risk of arrhythmias and sudden cardiac death (SCD). BrS is a challenging entity, in regard to diagnosis as well as arrhythmia risk prediction and management. Nowadays, asymptomatic patients represent the majority of newly diagnosed patients with BrS, and its incidence is expected to rise due to (genetic) family screening. Progress in our understanding of the genetic and molecular pathophysiology is limited by the absence of a true gold standard, with consensus on its clinical definition changing over time. Nevertheless, novel insights continue to arise from detailed and in-depth studies, including the complex genetic and molecular basis. This includes the increasingly recognised relevance of an underlying structural substrate. Risk stratification in patients with BrS remains challenging, particularly in those who are asymptomatic, but recent studies have demonstrated the potential usefulness of risk scores to identify patients at high risk of arrhythmia and SCD. Development and validation of a model that incorporates clinical and genetic factors, comorbidities, age and gender, and environmental aspects may facilitate improved prediction of disease expressivity and arrhythmia/SCD risk, and potentially guide patient management and therapy. This review provides an update of the diagnosis, pathophysiology and management of BrS, and discusses its future perspectives.

INTRODUCTION

Brugada syndrome (BrS) is an inherited cardiac disease, characterised by a typical ECG pattern and an increased risk of (supra)ventricular arrhythmias and sudden cardiac death (SCD) in relatively young and otherwise healthy individuals.[1 2] BrS is a challenging entity in terms of diagnosis, arrhythmia risk prediction and management. Progress in our understanding of the genetic and molecular pathophysiology is hindered by the absence of a true gold standard, with the clinical definition still changing over time. We here review the latest insights into the diagnosis, epidemiology, genetics, pathophysiology, risk stratification and management of BrS, as well as critical areas for (future) research.

CLINICAL PRESENTATION AND DIAGNOSIS

Historically, patients with BrS typically presented with syncope or (aborted) SCD in addition to the characteristic coved-type ST-segment in the right precordial ECG leads. However, at present, most new patients are asymptomatic with the typical ECG features identified coincidentally, following family screening, or after provocation testing with sodium channel-blocking drugs. Over the years, the definition and diagnostic criteria for BrS have been adjusted, with the most recent expert consensus statement recommending the following criteria (figure 1A)[3]: (1) a spontaneous type-1 (coved-type) BrS-ECG, or (2) a type-1 BrS-ECG unmasked by sodium channel blockers or fever, but only when having a type-2 or type-3 ECG (figure 2) at baseline and when accompanied by at least one additional criterion from the 'Shanghai Score System' (figure 1B).[3] Importantly, other conditions that may explain the coved-type ECG, so-called phenocopies (figure 3A), should be excluded. Additional ECG features may be helpful to identify a 'true' BrS-ECG (figure 3B).[4] Previous guidelines did not require additional criteria for patients with drug-induced type-1 ECG, thereby possibly overdiagnosing BrS.[5 6] Given the estimated rate of 5% positive tests in healthy subjects and the life-changing consequences of false-positive tests,[7] sodium channel blocker challenge should only be performed in patients with clinical suspicion of BrS in the absence of a spontaneous type-1 ECG.[3] Clearly, this matter is subject to interpretation. In our view, previous arrhythmias or cardiac arrest suggestive of BrS (eg, during fever), a family history of BrS or unexplained SCD, and a suspicious ECG (type-2, type-3) denote indications for provocation testing. In some of these patients, a provocation test might be considered before initiating therapy with sodium channel-blocking drugs (eg, psychotropic drugs). In general, however, the threshold for provocation testing in asymptomatic patients with slightly abnormal coincidental ECG findings (eg, (incomplete) right bundle branch block, benign right precordial 'early repolarisation') should be high. In children, provocation testing should be used only in highly suspicious cases; recommendation of preventive lifestyle measures should be considered as an alternative to delay provocation testing. Inducibility of sustained polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF) at the right ventricular (RV) outflow tract (RVOT) during electrophysiological study (EPS) may support a BrS diagnosis but should not be considered informative by itself (see [3]). Similarly, genetic testing is only partly informative since a negative test cannot exclude BrS (see below).

The estimated BrS prevalence has changed over time, due to refinements of its definition and more frequent family screening. The prevalence of adult BrS defined as having a spontaneous type-1 ECG is now estimated at 0%–0.10% in Europe/USA and 0%–0.94% in Asian countries (figure 4)[8 9]; the latter is likely explained by genetic predisposition. Overall, there is a male predominance (up to 90%).[3] The first symptoms typically occur in the third–fourth decade of life,[10] and may range from syncope to SCD; due to polymorphic VT/VF triggered by short-coupled ventricular extrasystoles.

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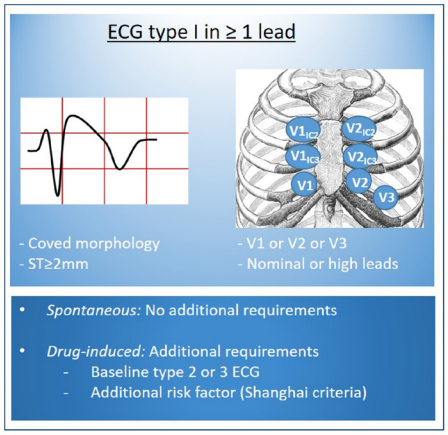
A


ECG type I in ≥ 1 lead
- Coved morphology
- ST≥2mm
- V1 or V2 or V3
- Nominal or high leads
• Spontaneous: No additional requirements
• Drug-induced: Additional requirements
- Baseline type 2 or 3 ECG
- Additional risk factor (Shanghai criteria)

B

Shanghai Score System	Points
I. ECG (12-Lead/Ambulatory)*	
A. Spontaneous type 1 Brugada ECG pattern at nominal or high leads	3.5
B. Fever-induced type 1 Brugada ECG pattern at nominal or high leads	3
C. Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge	2
II. Clinical History*	
A. Unexplained cardiac arrest or documented VF/polymorphic VT	3
B. Nocturnal agonal respirations	2
C. Suspected arrhythmic syncope	2
D. Syncope of unclear mechanism/unclear etiology	1
E. Atrial flutter/fibrillation in patients <30 years without alternative etiology	0.5
III. Family History*	
A. First- or second-degree relative with definite BrS	2
B. Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a first- or second-degree relative	1
C. Unexplained SCD >45 years in first- or second- degree relative with negative autopsy	0.5
IV. Genetic Test Result*	
A. Probable pathogenic mutation in BrS susceptibility gene	0.5
Score (requires at least 1 ECG finding) ≥3.5: Probable/definite BrS 2–3: Possible BrS <2: Non-diagnostic	

*Only award points once for highest score within this category

Figure 1 Diagnosis of Brugada syndrome (BrS) according to the latest expert consensus report[3]: (A) flow chart displaying criteria; (B) Shanghai Score System which includes additional risk factors requiring BrS diagnosis. SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

Notably, the majority of newly diagnosed patients are asymptomatic (64%) or have a history of syncope (30%), while only a small proportion (6%) present with cardiac arrest.[11] However, an unknown proportion of SCD cases with BrS remain undiagnosed.

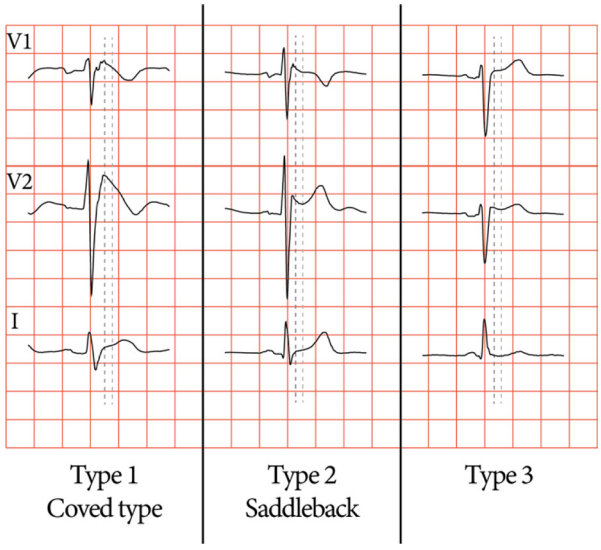


Figure 2 Brugada ECG types. Type-1: coved STT morphology in lead V2 with J-point elevation (dark grey line) of ≥0.2 mV (≥2 mm) and a terminal ST-segment elevation (light grey line, J+60 ms) also ≥0.2 mV (≥2 mm). Note the PR interval and wider QRS complex, wide and deep S in lead I, and fractionation in the right precordial ECG leads. Type-2: saddleback STT morphology in lead V2 with J-point elevation (dark grey line) of ≥0.2 mV (≥2 mm) and a terminal ST-segment elevation (light grey line, J+60 ms) ≥0.1 mV (≥1 mm), followed by a positive T wave. Note the less wide and deep S-wave in lead I, less prominent fractionation. This patient developed a type-1 ECG on ajmaline provocation. Type-3: saddleback STT morphology in lead V2 with J-point elevation (dark grey line) of ≥0.2 mV (≥2 mm) and a terminal ST-segment elevation (light grey line, J+60 ms) <0.1 mV (<1 mm). Note the absence of a wide deep S-wave in lead I and no obvious fractionation. This patient developed a type-1 ECG on ajmaline provocation.

Patients with BrS may also display atrial fibrillation/flutter and cardiac conduction abnormalities.[3 9] Arrhythmias and SCD typically occur during episodes of vagal predominance and/or bradycardia, that is, during rest or sleep (nocturnal agonal breathing).[3 9] The type-1 ECG pattern is often intermittently present, can be unmasked during the aforementioned conditions and is directly linked to the occurrence of arrhythmias.[3] Predisposing factors furthermore include electrolyte imbalances, hyperthermia/fever and sodium channel-blocking drugs (see www.brugadadrugs.org).[12] In addition to polymorphic VT/VF inducibility at the RVOT, epicardial mapping studies have demonstrated abnormal low voltages, prolonged ventricular potentials and fractionated late potentials in the epicardial layer of this region.[13] In addition, (subtle) structural abnormalities such as fibrosis, particularly in the RV/RVOT, have been reported, including occasionally inflammatory changes and RV fatty infiltration. These are typically associated with arrhythmogenic cardiomyopathy (ACM/ARVC), and an overlap in clinical as well as molecular features between BrS and ACM/ARVC is increasingly recognised.[14 15]

GENETICS

Numerous mutations in the *SCN5A* gene encoding the cardiac sodium channel ($Na_V1.5$) have been identified in patients with BrS, which create either less or dysfunctional $Na_V1.5$ channels at the cell membrane, resulting in a decreased sodium current.[16] However, patients with *SCN5A* mutation-positive BrS show a broad variability of symptom severity and age of onset (variable disease expression), and often have family members with the same mutation who are asymptomatic (incomplete penetrance).[17] Conversely, some patients with BrS with a pathogenic *SCN5A* mutation have family members with a BrS-ECG who do not carry the same familial *SCN5A* variant.[17] Moreover, within the healthy population, rare (missense) *SCN5A* variants are found in 2% of Caucasians and 5% of non-Caucasians.[18] Thus, the question remains whether *SCN5A* mutations are actually causal, or merely disease modifiers. Clearly, other genes play a role, as only about 21% of patients with BrS carry a potential pathogenic *SCN5A* mutation.[18] Rare variants in >20 other genes (figure 5A) have been identified in patients with BrS, leading to

A

Category	Conditions
ECG abnormalities	Atypical RBBB, Early repolarization
Electrolyte abnormalities	Hyper- and hypokalemia, Hyponatremia
Cardiomyopathy	Ventricular hypertrophy, ARVC/ACM
Infectious	Acute pericarditis/myocarditis
Ischemic	Myocardial ischemia or infarction of right ventricle
Pulmonary	Pulmonary thromboembolism
Drugs	Antiarrhythmics Class IA/1C, Antianginals, Antihistamines, Tricyclic antidepressants, Propofol, Alcohol intoxication, Cannabis
Other	Dissecting aortic aneurysm, Myotonic dystrophy Mechanical compression of RVOT (e.g. pectus excavatum), Hyperthermia, Hypothermia

B

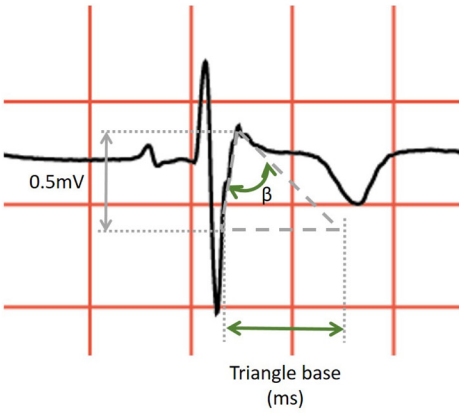


Figure 3 (A) Examples of phenocopies of BrS.[3] (B) Two tools which may be useful to identify a true BrS ECG: (I) a right precordial 'ß angle' >58°, that is, the angle of the terminal r, or (II) a duration >160 ms of the base of a triangle at 0.5 mV from the terminal high take-off in lead V1 or V2. These features have been shown to predict a positive ajmaline test.[4] ACM, arrhythmogenic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; RBBB, right bundle branch block; RVOT, right ventricular outflow tract.

either reduced inward sodium or calcium current or increased outward potassium current, but *SCN5A* remains the only undisputed causal gene .[19] While BrS was initially thought to be inherited as a monogenic, autosomal dominant disease requiring only one mutation, it is now considered more likely to encompass an oligogenic or polygenic inheritance, in which multiple 'genetic modifiers' either exacerbate or alleviate the phenotypical expression of the primary genetic defect (figure 5B).[14] These modifiers can be rare variants with a large effect size, or common variants carrying a small effect size. Additionally, common variants (polymorphisms) may modulate BrS risk and/or phenotype severity: the most common sodium channel polymorphism H558R has been shown to increase functional expression of *SCN5A* and mitigate phenotype severity in patients with BrS.[20] Inversely, a set of six polymorphisms in the *SCN5A* promotor region, occurring in 22% of Asians, was associated with a reduced $Na_V1.5$ expression and conduction delay.[21] A genome-wide association study (GWAS), comparing BrS patients with healthy controls, identified three alleles (comprising the *SCN5A*, *SCN10A* and *HEY2* genes) which solitarily increased BrS risk, as well as additively.[22] Importantly, such GWAS can also identify non-coding risk variants (located at intronic or regulatory DNA regions), that are not routinely screened for.[14] Moreover, these common variants can facilitate development and application of a polygenic risk score (as further discussed in the "Risk stratification" section).

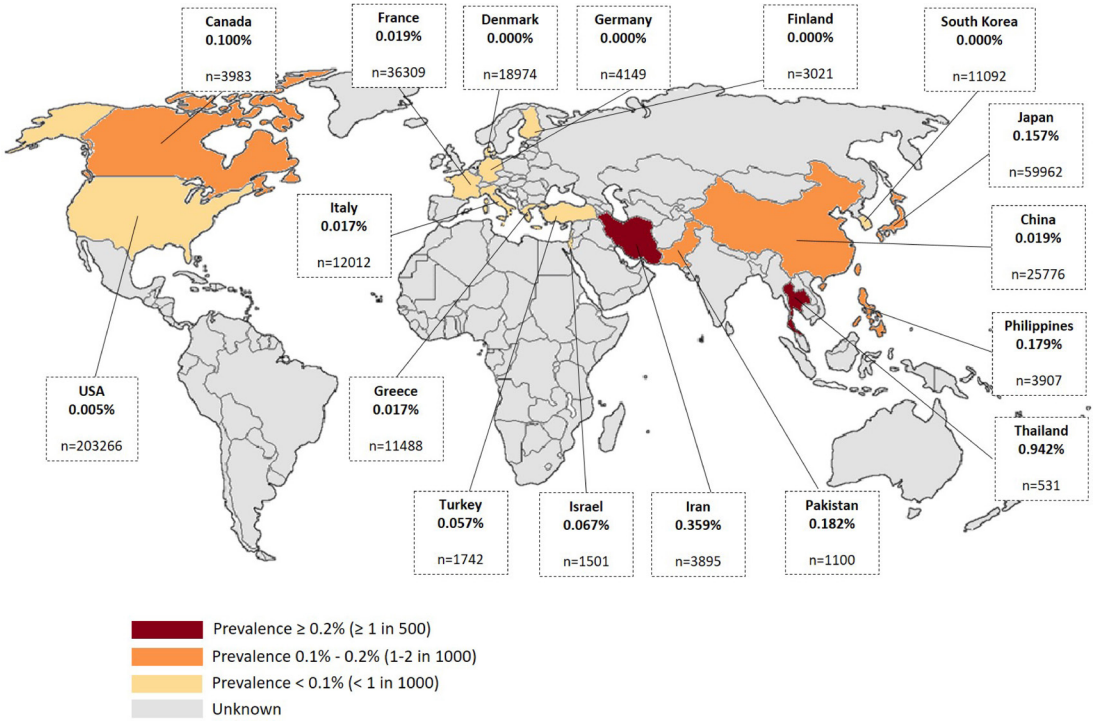


Figure 4 Overview of global prevalence of Brugada syndrome, defined as a spontaneous type-1 ECG pattern (reproduced with updated data with permission[8 9]). Prevelence depicted by the percentage (%) of the total number of indviduals (n) studied by combining different studies.

A

Gene	Protein/pathway
SCN5A, SCN10A	Sodium channel α-subunit
SCN1B, SCN3B	Sodium channel β-subunit
GPD1L, RANGRF	Sodium channel trafficking
CACNA1C, CACNB2	Calcium channel subunit
KCNE3, KCND3	Transient outward potassium current
KCNJ8, ABCC9	ATP-sensitive potassium channel

B

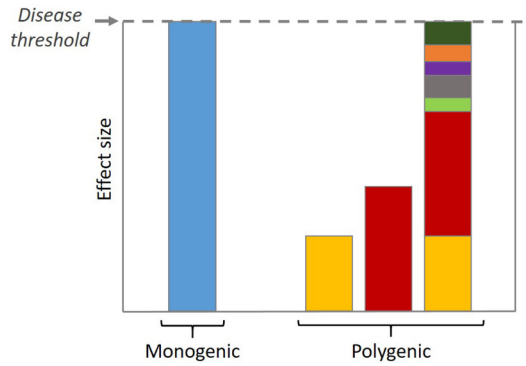


Figure 5 (A) In patients with Brugada syndrome (BrS), rare variants have been identified in various genes encoded by mostly ion channel proteins but also proteins involved in other pathways; examples are listed here.[16] (B) In addition, common variants contribute to BrS, which is increasingly considered to be polygenic. Here, multiple genetic variants together increase disease susceptibility, eventually reaching threshold by which the disease is exposed. These can be rare variants with a large effect size (represented by the yellow and red blocks), or common variants carrying a small effect size (blocks of other colours).

PATHOPHYSIOLOGY

Over the years, both enhanced transmural dispersion in repolarisation[23] as well as altered depolarisation with conduction slowing[24] particularly within the RV/RVOT have been proposed to underlie the ECG pattern and arrhythmogenesis in BrS (as detailed in figure 6A, and reviewed elsewhere[25]). However, while originally defined as a purely electrical disorder, cardiac structural abnormalities are now increasingly considered relevant.[26] Although routine cardiac echocardiography often shows a normal heart,[1] subtle abnormalities have been observed in

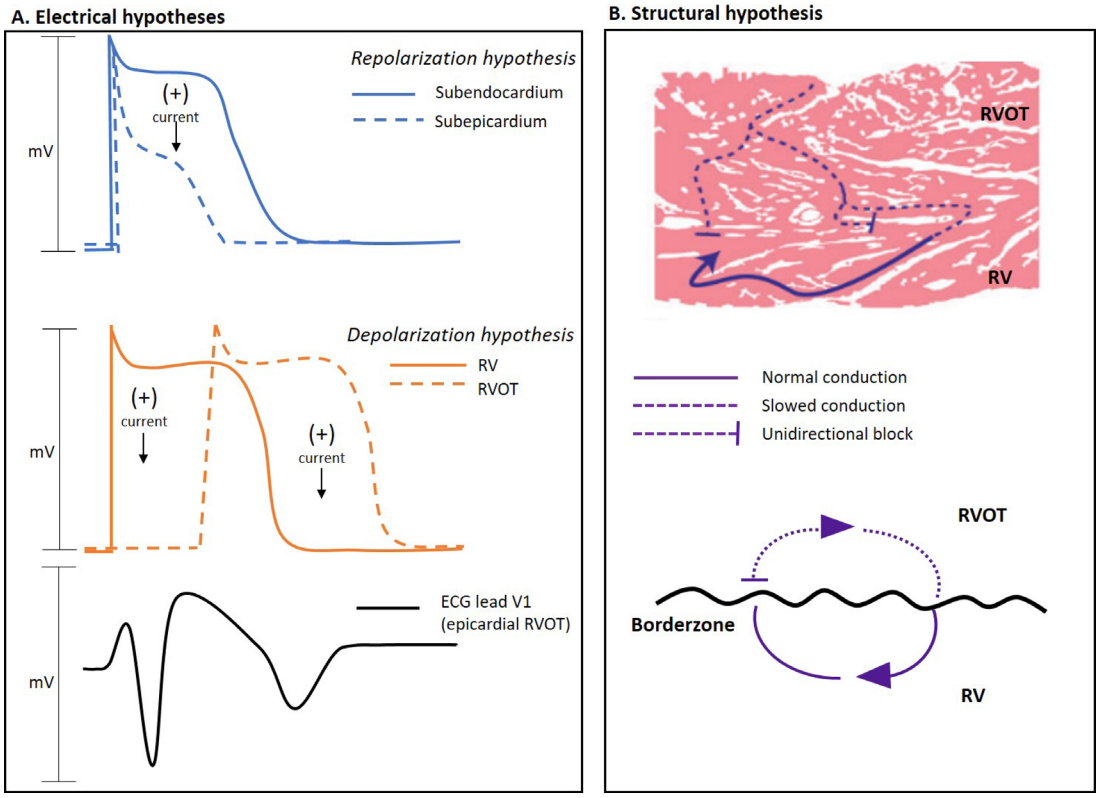


Figure 6 Pathophysiological mechanisms of BrS. (A) Proposed electrical mechanisms. Repolarisation hypothesis (upper panel): a transmural voltage gradient is created by the intrinsically increased subepicardial outward potassium current (I_{to}) combined with a pathologically decreased inward sodium current. Positive current flows from subendocardium to subepicardium during phase 2 of the action potential, which may lead to phase 2 re-entry. Depolarisation hypothesis (lower panel): altered depolarisation with subsequent conduction delay due to reduced sodium current and/or fibrosis is most prominent in the RVOT, creating a voltage gradient and a consequent positive current flowing from RV to RVOT during depolarisation, and a current in opposite direction following repolarisation of the RV. These are observed as, respectively, a positive and negative deflection on the RVOT ECG recording. (B) Structural abnormalities. Due to fibrosis and conduction delay, a current-to-load mismatch arises, causing unidirectional conduction block at the borderzone of RVOT and RV. This creates a substrate for re-entry, in which the slowed conduction in the RVOT (dashed purple line) allows to maintain this re-entry circuit. BrS, Brugada syndrome; RV, right ventricular; RVOT, RV outflow tract.

patients with BrS using MRI and CT, including RVOT dilation, reduced RV ejection fraction and RV wall motion abnormalities.[27] These latter may represent structural deformities and/or electrical conduction slowing with consequently delayed myocardial contraction. Biopsy studies have furthermore found subtle cardiomyopathic alterations in patients with BrS (after excluding ARVC),[26] in addition to higher levels of fibrosis and reduced expression of the gap junction protein connexin-43 in the RV/RVOT.[28] These structural changes may be the cause or the consequence of electrical disturbances and/or ion channel dysfunction. For instance, a reduced number of sodium channels may affect other (structural) proteins co-localising and/or interacting with $Na_v1.5$ at the cell–cell junction (intercalated disk); this may also explain the observed link between *SCN5A* mutations and ACM/ARVC.[14 15] However, since most patients with BrS do not carry *SCN5A* mutations, other as yet unknown (molecular) mechanisms are likely involved. Structural abnormalities could explain onset of BrS symptoms in mid-life, indicating that the underlying pathology needs time to develop. In contrast, electrical disturbances may be mostly responsible for the young-onset symptoms in children with BrS, as suggested by the high prevalence of *SCN5A* mutations in these patients.[29] Independent of their origin, structural abnormalities may cause conduction block and facilitate re-entrant arrhythmias (figure 6B).[26] Indeed, catheter ablation of surviving myocardium between fibrotic tissue can eliminate this arrhythmogenic substrate, thereby erasing the Brugada ECG pattern and reducing arrhythmic burden.[13 28]

In patients with BrS, sodium channel-blocking drugs, such as most class I anti-arrhythmics and tricyclic anti-depressants, can be pro-arrhythmic for obvious reasons.[12] Another major trigger is fever,[30] most likely by inducing/enhancing conduction slowing in the RVOT.[31] Since most arrhythmic events occur during rest, sleep or following large meals, changes in vagal tone might increase arrhythmic risk.[26 32] Accordingly, sympathetic drugs (isoproterenol) reduced ST-elevation whereas parasympathetic drugs (edrophonium) augmented ST-elevation in patients with BrS.[33] Potential mechanisms include effects on ion channels, and cardiac autonomic imbalance with abnormal presynaptic norepinephrine regulation.[26] Finally, the markedly higher prevalence in men suggests that hormones are involved in BrS pathophysiology, especially in adults (male:female ratio of >10 in adults vs 2 in children).[10] This may be (partly) explained by gender differences in potassium channel expression (thereby affecting I_{to}) as well the differential effects of hormones on ion channels (see [34]).

A reduced RVOT conduction reserve has been proposed as a final common pathway for all above-mentioned mechanisms. This conduction reserve is determined by age, gender and ethnicity, the presence of structural tissue abnormalities and/or ion channel (dys)function, and influenced by modulators such as fever, drugs and altered vagal tone, jointly contributing to the Brugada phenotype.[16 25] Dispersed repolarisation between the subepicardial and endocardial layers, due to fibrotic uncoupling, may play an additional contributing role. Given their unique structural features, including transmural fibre orientation, non-vascular clefts and increased collagen content, the RV and in particular the RVOT are likely more sensitive to these mechanisms by creating a 'current-to-load mismatch'.[25 26] Ultimately, electrophysiological, structural and genetic factors together with environmental elements will determine BrS phenotype expression and severity (figure 7).

RISK STRATIFICATION

Risk of future VT/VF is highest in patients with BrS with a history of cardiac arrest, arrhythmic syncope or ventricular arrhythmias. In those with prior cardiac arrest, cardiac event rates (documented sustained VT/VF, or SCD) of 7.7% per year,[11] up to 48% in 10 years have been reported.[35] This is substantially lower in asymptomatic patients and patients with previous syncope, having yearly cardiac event rates of, respectively, 0.5% and 1.9%.[11] Nevertheless, asymptomatic patients still have an increased risk of arrhythmic events and a lower survival than the healthy population,[11 35] and 61%–80% of patients with BrS with cardiac arrest were previously asymptomatic.[10 36] Therefore, better risk markers are needed to further decrease event rates in asymptomatic individuals. The value of EPS in this respect has been debated. The FINGER registry, for example, did not find a predicting role for family history of SCD or inducibility during EPS.[11] This is in contrast with a pooled analysis including seven more studies that did find a positive predictive role for inducibility during EPS, although the lack of induction at EPS did not reliably identify low-risk patients.[37] Less invasive prediction methods using ECG markers such as a type-1 ECG pattern in peripheral leads, QRS fragmentation, S-wave in lead I, aVR sign and early repolarisation pattern showed association with increased VT/VF during follow-up, but their prognostic significance requires further validation.[38]

The presence of an *SCN5A* mutation has also been proposed as a risk factor for arrhythmia/SCD, although results are

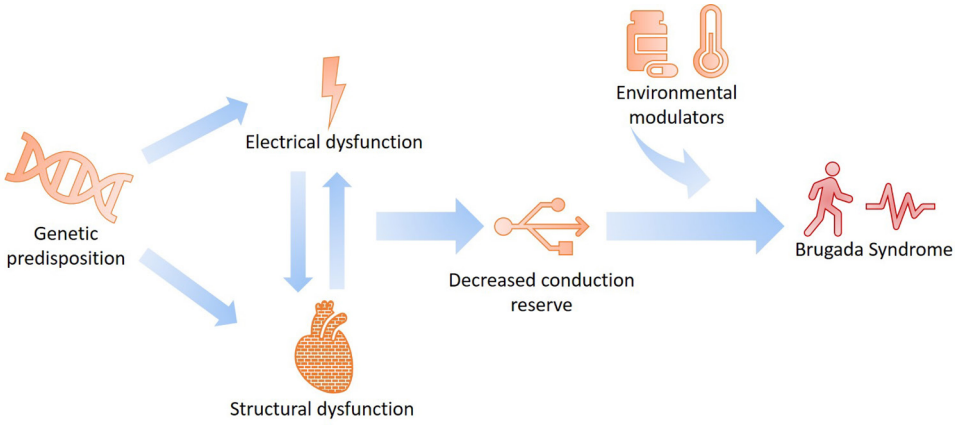


Figure 7 Integrative pathophysiological overview. Genetic predisposition, electrical and structural dysfunction, and environmental factors contribute to the Brugada syndrome phenotype.

inconsistent.[11 29] More specifically, carriers of a truncating mutation (ie, a premature stopcodon) displayed higher rates of syncope compared with patients having missense mutations that lead to less severe sodium current reduction, underlining the potential relevance of mutation type.[39] Although the predictive properties of *SCN5A* mutations highly depend on age and ethnicity, its presence is part of the Shanghai risk score (figure 1). Importantly, the identification of a pathogenic mutation allows cascade screening among family members. Identified mutation carriers can then be further evaluated diagnostically, and if needed managed by lifestyle modification and additional therapy in selected cases.[40] The role of multiple common and rare variants in BrS is moreover increasingly recognised (figure 5). A polygenic risk score of their cumulative effect (summing up each hazardous and protective allele, weighted by its effect size) has been shown to be predictive of the response to sodium channel blocker provocation, and may be of potential future value for predicting arrhythmias and SCD.[41]

Given the limited predictive power of single parameters, risk scoring models that incorporate multiple predictive factors have been proposed.[38] A prospective multicentre study of 1110 patients with BrS without previous cardiac arrest identified four main risk factors (probable arrhythmia-related syncope, spontaneous type-1 ECG, type-1 ECG pattern and early repolarisation in peripheral leads) with an additive effect.[42] Similarly, risk factor assessment using the Shanghai Score System has been shown to predict future arrhythmic events in the highest and lowest risk groups, but shows a low predictive value in the intermediate risk group (eg, asymptomatic patients with spontaneous type-I ECG), making clinical decision-making based on these scores problematic.[43] New scoring models focusing on this group, incorporating genetic, electrophysiological and environmental factors (including age and sex) are therefore needed.

MANAGEMENT AND THERAPY

All patients with BrS are advised to avoid potential triggers for VF and SCD, including certain (non-)cardiac drugs (www.brugadadrugs.org)[12] and excessive alcohol consumption, while fever should be aggressively treated with antipyretics.[5 40] The latter may also be particularly relevant for (COVID-19) vaccinations.[44] Notably, the data underlying drug–BrS interactions are imperfect, and balancing of risks is necessary, particularly when there are essential indications for the use of such drugs. Additional therapeutic measures depend on whether or not a patient is symptomatic (figure 8).

Symptomatic patients

All recent guidelines and expert consensus statements advise implantable cardioverter defibrillator (ICD) therapy for symptomatic patients with BrS (class I recommendation), but they differ in their definition of 'symptomatic'.[3 5 40 45] While agreeing that patients with previous cardiac arrest or documented sustained VT/VF require an ICD, they disagree on whether an ICD is advised for patients with a history of (undocumented) syncope. Here, thorough history taking is crucial in distinguishing arrhythmic from non-arrhythmic syncope. In a study by Olde Nordkamp *et al*, all 67 patients with BrS with presumed non-arrhythmic syncope (ie, preceded by specific situations such as prolonged standing, crowded surroundings, pain or emotional stress) stayed free of cardiac arrest during a 5-year follow-up period.[46] Recent ESC (European Society of Cardiology) syncope guidelines advise, in case of unexplained syncope, to consider an ICD in patients with spontaneous type-1 ECG, or an implantable loop recorder in patients with BrS with low risk of SCD (class IIa recommendation).[47] Although an ICD is the ultimate prevention for SCD, its benefits in low-risk patients are questionable, in addition to the risk of (potentially lethal) device-related complications (which may outweigh benefits) and a high prevalence of inappropriate shocks.[35] These risks are even higher in children, with 20% of them experiencing inappropriate shocks and 14% device-related complications.[48] When ICD therapy is refused, contraindicated or insufficient (eg, frequent shocks), long-term treatment with quinidine can have significant benefit.[5 40] Quinidine may also be considered in asymptomatic patients with risk factors, although its efficacy here is still uncertain. Chronic drug treatment using bepridil, cilostazol and denopamine is also reported to suppress development of ventricular arrhythmias.[3] Unfortunately, these anti-arrhythmic drugs are not always

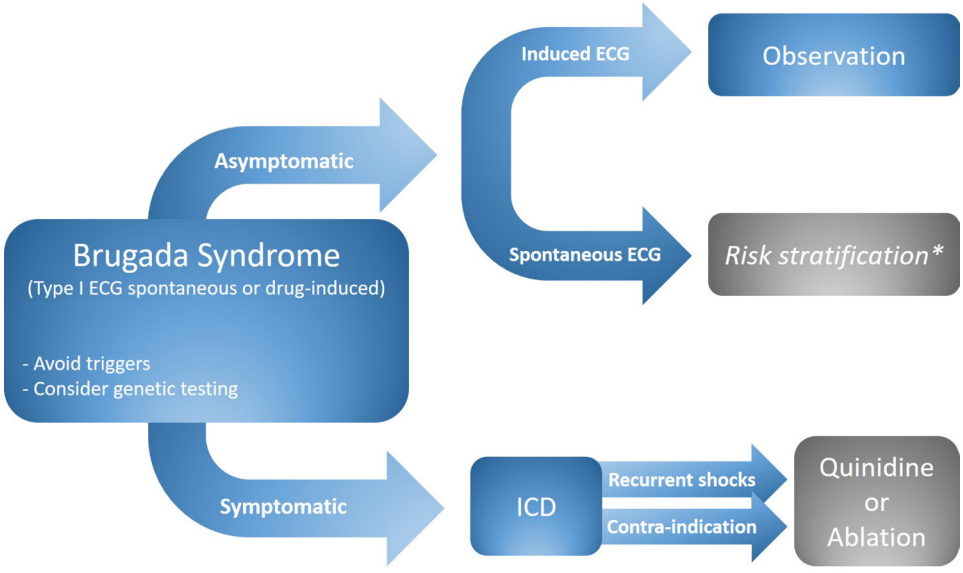


Figure 8 Management of BrS. Blue indicates recommendation I, grey indicates recommendation IIa or IIb, according to latest guidelines.[5 40 45] Management of asymptomatic patients with spontaneous type-1 ECG (*) is debated; risk stratification options such as EPS may be considered. BrS, Brugada syndrome; EPS, electrophysiological study; ICD, implantable cardioverter defibrillator.

effective, available[49] or convey intolerable side-effects. Catheter ablation of the arrhythmogenic substrate may be considered,[5 40 45] as it may prevent premature ventricular contractions that trigger arrhythmias, thereby reducing further recurrences of ventricular tachyarrhythmias.[28] However, this approach appears more sensible in patients at very high risk of events (ie, with repetitive VT/VF), while its usefulness in lower risk patients remains unclear.[50]

Acute treatment

When patients with BrS present with VTs or arrhythmic storm, acute treatment with isoproterenol or quinidine should be considered.[5 45] Crucially, frequently used anti-arrhythmic drugs such as amiodarone and procainamide can do serious harm in this setting due to their sodium channel-blocking properties. All potential triggers, such as electrolyte disturbances and fever, should be aggressively corrected.

Asymptomatic patients

As the majority of patients are now found through genetic screening, management of asymptomatic patients is becoming increasingly important. In asymptomatic patients, the only clear independent risk factor for ventricular arrhythmias is a spontaneous type-1 ECG.[11] The value of a positive EPS (inducible VF or sustained VT using single and double extrastimuli) and other clinical or genetic variables in asymptomatic patients with BrS remains unresolved. Generally, an ICD is not recommended in asymptomatic patients, and avoidance of triggers is the only treatment.

CURRENT CHALLENGES AND FUTURE PERSPECTIVES

BrS remains a challenging disease entity, both in terms of diagnosis as well as arrhythmia risk prediction and management. Its underlying pathophysiological mechanisms remain incompletely understood, hampering the development of effective mechanism-based therapies. Novel approaches to evaluate the arrhythmogenic substrate include ECG imaging to map epicardial electrical activity with high resolution, and MRI visualisation of subtle structural alterations in the RVOT. Advances in ICD therapy such as subcutaneous and leadless devices might reduce complications, but may not be suitable for highly symptomatic patients that benefit from anti-tachycardia pacing. The change in thinking from primary electrical disease to a (partly) structural disease has also instigated new therapies such as targeted ablation. BrS incidence continues to rise due to (genetic) family screening, and asymptomatic patients currently represent the majority of newly diagnosed BrS cases. While their arrhythmia risk is relatively low, some may still experience cardiac arrest and hence risk stratification in these patients (particularly children and young adolescents) remains essential yet challenging. Recent studies have demonstrated the potential usefulness of risk scores to identify high-risk patients; in addition, less conventional clinical tests such as the ‘full stomach challenge’ deserve further investigation.[32] The identification of a polygenic basis for BrS and the potential role of common genetic variants provide future opportunities for applying polygenic risk scores for individual risk prediction. Further development and validation of models that incorporate clinical and genetic factors, comorbidities, age and gender, and environmental factors will facilitate prediction of arrhythmia/SCD risk, and ultimately guide patient management and therapy.

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